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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/445,223	12/06/1999	DAVID WALLACH	WALLACH=24	9660

1444 7590 04/21/2006

BROWDY AND NEIMARK, P.L.L.C.  
624 NINTH STREET, NW  
SUITE 300  
WASHINGTON, DC 20001-5303

EXAMINER

DAVIS, MINH TAM B

ART UNIT PAPER NUMBER

1642

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/445,223

Applicant(s)

WALLACH ET AL.

Examiner

MINH-TAM DAVIS

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 30 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 5-8, 11, 23, 24, 44-48, 51 and 54-57 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 5-8, 11, 23, 24, 44, 46-48, 51 and 54-57 is/are rejected.
- 7) ☒ Claim(s) 45 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Accordingly, claims 5-8, 11, 23-24, 44-48, 51, 54-57 are being examined.

The following are the remaining rejections.

### **MISCELLANEOUS**

It is noted that the sequence listing submitted on 12/06/1999 is not readable after scanning.

It is requested that Applicant resubmits a clear copy of the sequence listing of 12/06/1999, and a returned receipt, for scanning.

### **SPECIFICATION**

It is noted that the specification submitted on 02/28/02 seems to be a substitute of the original specification of 12/06/1999. However, no marked-up copy is found.

Applicant is required to submit a marked-up copy of a substitute specification.

A substitute specification submitted under section 1.125 must be submitted with markings showing all the changes relative to the immediate prior version of the specification of record. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters.

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The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. An accompanying clean version (without markings) must also be supplied. Numbering the paragraphs of the specification of record is not considered a change that must be shown pursuant to this paragraph.

### **OBJECTION**

Claim 45 appears to be free of prior art but are objected to as being dependent upon a rejected base claim, claim 44, but would be allowable if rewritten in independent forms.

### **REJECTION UNDER 35 USC 112, SECOND PARAGRAPH, NEW REJECTION**

Claims 5-8, 11, 23, 44, 46-48, 54-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5-8, 11, 23, 44, 46-48, 54-55 are indefinite for the use of the language "potentiating" cell death in claims 11, 44. It is not clear what "potentiating" cell death means, especially in view that the specification does not define "potentiating" cell death.

### **REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION**

Claims 5-8, 11, 23-24, 44, 46-48, 51, 54-57 remain rejected under 35 USC 112, first paragraph, for lack of a clear written description of 1) an antisense sequence of a DNA sequence encoding SEQ ID NO:1 effective to block the expression of SEQ ID

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NO:1 upon use, 2) a DNA sequence encoding a analog of SEQ ID NO:1, with no more than 10 changes in the amino acid sequence of SEQ ID NO:1, each said change being a substitution, deletion or insertion of a single amino acid, which analog potentiates cell death, and 3) a fragment of SEQ ID NO:1, which fragment potentiates cell death, for reasons already of record in paper of 07/29/05.

A. Regarding antisense, Applicant argues that Written description guidelines teaches that any full length complement of a target mRNA inhibits the function of the mRNA and is therefore an antisense oligonucleotide, and that a disclosure of a coding sequence with the statement that the invention includes antisense oligonucleotides as an implicit disclosure that the full length complement of SEQ ID NO:1 is an antisense oligonucleotide.

Applicant argues that the Written description guidelines teaches the sequence (SEQ ID NO:1) which defines and limits the structure of any effective antisense molecules such that one would be able to immediately envisage members of the genus embraced by the claim.

Applicant's arguments in paper of 01/30/06 have been considered but are not found to be persuasive for the following reasons:

It is noted that as written the claimed antisense sequence is not limited to the full length complement of the DNA sequence encoding the polypeptide SEQ ID NO:1, or oligonucleotide antisenses thereof, that could block the expression of the DNA sequence **in vitro**.

**The claims encompass a subgenus of antisense sequences of any length, including oligonucleotide antisense of 10 to 20 nucleotides in length, wherein said antisenses could block the expression of the DNA sequence *in vivo*.**

One would **not** be able to immediately envisage members of the subgenus embraced by the claims in view of the following teaching in the art. Branch, AD, 1998, TIBS 23: 45-50 teaches that it is very difficult to predict what portions of an RNA molecule will be accessible to an antisense sequence *in vivo*, and therefore, rational design of antisense molecule is not possible. Branch further teaches that although antisense oligonucleotides could be screened *in vitro*, it is not clear whether the identified antisense oligonucleotides are effective *in vivo*, and that *in vitro* studies will not always predict *in vivo* efficacy (p.49, first column, last paragraph, bridging second paragraph, and last column, second paragraph). In addition, Branch also teaches that although some antisense molecules had some clinical value through non-antisense effects, the non-antisense effects are not predictable and these effects must be explored on a case-by-case basis (p.50, first column). Further, even if an antisense oligonucleotide could be successfully used *in vitro* to inhibit the expression of a gene, it is unpredictable that said antisense oligonucleotide could be successfully used *in vivo*, because 1) successful application of antisense therapy *in vivo* has been extremely limited, and that there are only a few reports of modulation of various pathological conditions by antisense therapy in rodents, and 2) even if the biological significant amounts of antisense molecules reach target cells, and bind to selected target sites on

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mRNA, a subsequent effect on regulation of translation is not guaranteed, as taught by Weiss, 1998 (US 5,840,708).

Thus, although one can routinely screen for in vitro oligonucleotide antisenses, one cannot predict which small oligonucleotide antisense of the claimed DNA sequence encoding SEQ ID NO:1 will be accessible to the sequence in vivo and effective in inhibiting the function of the sequence *in vivo*.

The specification however does not disclose which small oligonucleotide antisenses of the claimed DNA sequence inhibit the expression or function of the claimed DNA sequence or the encoded polypeptide thereof in vivo.

The teaching in the Written description guidelines is not applicable to the instant claims, which encompass an undisclosed, specific subgenus of antisenses, wherein said antisenses could block the expression of the DNA sequence in vivo.

In view of such unpredictability, the species full length complement of SEQ ID NO:1, and the species antisenses that inhibit the function of the claimed DNA sequences in vitro are not representative species of the claimed subgenus of oligonucleotide antisenses that could block the expression of the DNA sequence in vivo.

In view of the above, the specification and the claims do not meet the requirement of 112, first paragraph, written description. One would conclude that Applicant did not have possession of the claimed genus of antisense sequences being effective to block the expression of the encoded polypeptide upon use, which reads on in vivo use.

**B. Regarding written description of an analog of the polypeptide SEQ ID**

**NO:1**, Applicant argues that the specification discloses that “acceptable analogs are those which retain at least the prodomain (CARD). Applicant argues that ten single residues changes for a full length 540 residue polypeptide, the claimed analog would have greater than 98% sequence identity. Applicant argues that as taught by Example 14 in the Written description guidelines, one would conclude from the single species, SEQ ID NO:1, that the single species disclosed is representative of the entire genus, because all members have at least 95% structural identity to the reference sequence of SEQ ID NO:1 and have a specific activity, i.e. potentiating cell death.

Applicant’s arguments in paper of 01/30/06 have been considered but are not found to be persuasive for the following reasons:

It is noted that SEQ ID NO:1 does not by itself causes cell death, but enhances the level of cell death induced by FAS-R, p55 TNF-R or RIP (p.57, second paragraph) and that SEQ ID NO:1 does not have direct interaction with these cell death mediators (p. 62, second paragraph).

It is further noted that due to the indefinite language “potentiating cell death”, the function of potentiating cell death is not limited to enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP.

Thus because the function of potentiating cell death is not limited to enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP, there is no correlation between structure and the function of “potentiating” cell death.

Further, the Examiner takes note that **neither the CARD domain nor the kinase domain per se is always required for** enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP, because as shown in figure 5 of the instant application, although the mutants  $\Delta$  Nde and  $\Delta$  K of SEQ ID NO:1 containing the CARD domain, but with deleted kinase domain, retain some enhancing of the level of cell death induced by FAS-R, p55 TNF-R or RIP, however, the mutant  $\Delta$  CARD (without the CARD domain) also retain some enhancing of the level of cell death induced by FAS-R, p55 TNF-R or RIP.

Further, it seems that from figure 5, for the N-terminal fragments, a region that includes the kinase domain, and even up to the amino acid at position 374, is not sufficient for retaining some enhancing of the level of cell death induced by FAS-R, p55 TNF-R or RIP (see the mutant  $\Delta$ Xba in figure 5).

In other words, depending whether it is an N-terminal or a C-terminal fragment, the requirement for the N-terminal fragment, that includes the kinase domain is different.

Thus, even if the function of potentiating cell death were limited to enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP, there is no common structure that could be determined to be required for enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP, for the C-terminal fragments ( $\Delta$  Nde,  $\Delta$  K ) and the N-terminal fragment ( $\Delta$  CARD), that enhance the level of cell death induced by FAS-R, p55 TNF-R or RIP.

Thus, in view of a lack of a common structure correlated with function, the described analogs of SEQ ID NO:1 that enhance the level of cell death induced by FAS-

R, p55 TNF-R or RIP seem to be limited to the subgenus of analogs, wherein for the C-terminal analogs, no more than ten amino acids are deleted at the N-terminal end, up to the amino acid at position 314, and for the N-terminal analogs, no more than ten amino acids are deleted at the C-terminal end, up to the amino acid at position 455.

That is the described analogs are limited to the subgenus of a DNA sequence having 98% sequence identity with SEQ ID NO:1, wherein said DNA sequence encodes the amino acid sequence comprising amino acids 1-454, 244-540, or 315-540 of SEQ ID NO:1, and wherein said amino acid sequence enhances the level of cell death induced by FAS-R, p55 TNF-R or RIP.

**C. Regarding a fragment of SEQ ID NO:1, which fragment potentiates cell death,** Applicant argues that the CARD domain is necessary and sufficient to potentiate cell death, as shown by the fragments  $\Delta$  Nde and  $\Delta$  K in figure 5, which are representative of the genus of the claimed fragments that potentiate cell death.

Applicant argues that the issue of whether or not potentiation occurs by binding of CARD to Bcl2 is not critical to the question of whether this domain in SEQ ID NO:1 potentiates cell death.

Applicant's arguments in paper of 01/30/06 have been considered but are not found to be persuasive for the following reasons:

It is noted that due to the indefinite language "potentiating cell death", the function of potentiating cell death is not limited to enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP.

Thus because the function of potentiating cell death is not limited to enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP, there is no correlation between structure and the function of "potentiating" cell death.

Further, contrary to Applicant's arguments, the fragments  $\Delta$  Nde and  $\Delta$  K in figure 5 are not representative of the genus of the claimed fragments that potentiate cell death, because the **CARD domain per se is not always required for cell death potentiation**, as shown in figure 5 of the instant application, in which the mutant of SEQ ID NO:1,  $\Delta$  CARD (without the CARD domain) "potentiates" cell death, although with lower intensity as compared to that of the full length sequence, supra.

**The disclosed species  $\Delta$  Nde and  $\Delta$  K are not representative species of the claimed subgenus of fragments, because although they have a common structure, CARD, said common structure is not always required for potentiating cell death.**

It is noted that depending whether it is an N-terminal or a C-terminal fragment, the requirement for the N-terminal fragment, that includes the kinase domain is different, supra.

Thus, even if the function of potentiating cell death were limited to enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP, there is no common structure that could be determined to be required for enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP, for the C-terminal and N-terminal fragments, that enhance the level of cell death induced by FAS-R, p55 TNF-R or RIP.

Thus the described DNA sequence encoding a fragment of SEQ ID NO:1, said fragment enhances the level of cell death induced by FAS-R, p55 TNF-R or RIP seems to be limited to the subgenus of a DNA sequence consisting of a polynucleotide sequence encoding a polypeptide consisting of a fragment of SEQ ID NO:1, wherein said fragment comprises amino acids 1-454, 244-540, or 315-540 of SEQ ID NO:1.

The claims and the specification thus do not meet the standards, as shown in the examples of Lilly and Enzo, in view that the described three species are not representative species, and further in view that there is no correlation between structure and function, for reasons set forth above.

In summary, the claims and the specification do not meet the requirements of 112, first paragraph, written description, and one would conclude that Applicant did not have possession of the claimed fragments at the time the invention was made.

#### **REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE**

1. Claims 5-8, 11, 23, 44, 46-48, 54-55 remain rejected under 35 USC 112, first paragraph, because while being enabled for 1) a DNA sequence encoding SEQ ID NO:1, 2) a DNA sequence having 98% sequence identity with SEQ ID NO:1, wherein said DNA sequence encodes the amino acid sequence comprising amino acids 1-454, 244-540, or 315-540 of SEQ ID NO:1, and wherein said amino acid sequence enhances the level of cell death induced by FAS-R, p55 TNF-R or RIP, or 3) a DNA sequence consisting of a polynucleotide sequence encoding a polypeptide consisting of a fragment of SEQ ID NO:1, wherein said fragment comprises amino acids 1-454, 244-

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540, or 315-540 of SEQ ID NO:1, **the specification lacks enablement for 1) a DNA sequence encoding a analog of SEQ ID NO:1, with no more than 10 changes in the amino acid sequence of SEQ ID NO:1, each said change being a substitution, deletion or insertion of a single amino acid, which analog potentiates cell death, and 2) a fragment of SEQ ID NO:1, which fragment potentiates cell death,** for reasons already of record in paper of 07/29/05.

Applicant argues that based on figure 5, acceptable analogs are those which retain at least CARD domain, and one would target regions outside of the CARD domain to generate variants or fragments. Applicant argues that since the prodomain CARD structure is common for proteins involved in apoptotic signaling, one could even make conservative substitution for the CARD region.

Applicant's arguments in paper of 01/30/06 have been considered but are not found to be persuasive for the following reasons:

It is noted that due to the indefinite language "potentiating cell death", the function of potentiating cell death is not limited to enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP.

Thus because the function of potentiating cell death is not limited to enhancing the level of cell death induced by FAS-R, p55 TNF-R or RIP, there is no correlation between structure and the function of "potentiating" cell death, and one would not know how to make the claimed analogs or fragments, such that they would have the function of "potentiating" cell death.

Further, contrary to Applicant's arguments, the **CARD domain per se is not always required for cell death potentiation**, as shown in figure 5 of the instant application, in which the mutant of SEQ ID NO:1,  $\Delta$  CARD (without the CARD domain), also potentiates cell death, *supra*.

In view of the unpredictability of protein chemistry, as taught by Bowie et al, Burgess et al, Lazar et al, and Tao et al, all of record, which unpredictability applies as well to DNA sequences which encode proteins, one would not know how to make the claimed analogs or fragments, such that they would function as claimed, other than: 1) a DNA sequence having 98% sequence identity with SEQ ID NO:1, wherein said DNA sequence encodes the amino acid sequence comprising amino acids 1-454, 244-540, or 315-540 of SEQ ID NO:1, and wherein said amino acid sequence enhances the level of cell death induced by FAS-R, p55 TNF-R or RIP, and 2) a DNA sequence consisting of a polynucleotide sequence encoding a polypeptide consisting of a fragment of SEQ ID NO:1, wherein said fragment comprises amino acids 1-454, 244-540, or 315-540 of SEQ ID NO:1, and wherein said fragment enhances the level of cell death induced by FAS-R, p55 TNF-R or RIP.

Further, it would be undue experimentation for screening such analogs or fragments. Screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

**2. If Applicant could overcome the above 112, first paragraph, claim 8 is**

**still rejected under 112, first paragraph, because the amended claim 8 still reads on a host cell, which is non-naturally transformed by gene therapy.**

Rejection remains, because Applicant did not answer to this issue.

In view that gene therapy is unpredictable, as taught by Miller et al, Deonarain, Verma and Crystal, all of record, one cannot predict that the claimed host cell could be obtained.

**REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION**

Claims 24, 51, 56-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the full length complement of the polynucleotide sequence encoding SEQ ID NO:1, or an antisense thereof that effectively blocks the expression of SEQ ID NO:1 in vitro, does not reasonably provide enablement for an antisense sequence of a DNA sequence encoding SEQ ID NO:1 being effective to block the expression of SEQ ID NO:1 upon use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 24, 51, 56-57 are drawn to an oligonucleotide antisense sequence of a DNA sequence encoding SEQ ID NO:1 being effective to block the expression of SEQ ID NO:1 upon use.

Claims 24, 51, 56-57 encompass an oligonucleotide antisense sequence of a DNA sequence encoding SEQ ID NO:1 being effective to block the expression of SEQ ID NO:1 upon **in vivo** use, such as gene therapy.

The claims are not enabled, because although one can routinely screen for in vitro oligonucleotide antisenses, one cannot predict of which small oligonucleotide antisense of the claimed DNA sequence encoding SEQ ID NO:1 will be accessible to the sequence in vivo and effective in inhibiting the function of the sequence *in vivo*, in view of the teaching of Branch, 1998, and US 5,840,708, *supra*, and further in view that gene therapy is unpredictable, as taught by Miller et al, Deonarain, Verma and Crystal, all of record.

Further, it would be undue experimentation for screening the claimed antisenses. Screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

  
JEFFREY SIEW  
SUPERVISORY PATENT EXAMINER

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

April 05, 2006